

### **Claim Amendments**

Claim 1 has been amended to limit to chelating agents. Basis can be found at page 6 lines 11 to 21, plus page 4 lines 4 to 15 of the specification. Hence, applicants contend that no new subject matter has been added.

#### **1. CLAIM REJECTIONS: 35 U.S.C. § 103(a).**

Claims 1-14 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over the combination of Crane (US 5,951,952) with Yamaguchi (JP 11-99-99192 A), in further view of Schott Glaswerke (DE 29609958) or Walther (US 6,200,658).

The Examiner's logic is that the  $^{99m}\text{Tc}$  complex of *tert*-butyl-isonitrile ligand of Crane corresponds to a radiopharmaceutical comprising an organic ligand as defined in previous claim 1. The additional features of present claim 1, in particular the container having a silica coating on the inner surface, are allegedly then provided in an obvious manner by Yamaguchi, Schott and/or Walther.

Applicants refer to revised claim 1, which now has the essential feature that the organic ligand must be a chelating agent having 2 or more metal donor atoms chosen from N, O, S, P or Se. Applicants contend that the person skilled in the art would know that a chelating agent, by definition, forms so-called "chelate rings" in which the pair of metal donor atoms of the ligand both coordinate to the metal. This is illustrated in the present specification at page 6 equation (iii) [lines 11-22], wherein A is the metal donor site.

The Examiner has shown the chemical structure of *tert*-butyl-isonitrile. It is clear that the ligand falls outside the definition '2 or more metal donor atoms chosen from N, O, S, P or Se' - since it only has a single heteroatom (N). Indeed the metal coordination of *tert*-butyl-isonitrile occurs *via* the carbon atom of the C≡N triple bond, not the N heteroatom. Hence, isonitrile ligands are outside the scope of present revised claim 1 and even analogues thereof based of such ligands having 2 or more isonitrile donor groups would also fall outside the claim scope because such ligands do not have the necessary combination of heteroatom metal donor atoms.

In addition, the person skilled in the art would know that such isonitriles are monodentate, i.e. coordinate only *via* the carbon atom of the isonitrile group. Hence, *tert*-butyl-isonitrile falls outside the definition of the term 'chelating agent'. The person skilled in the art would also know that the C≡N triple bond confers great rigidity, and thus constrains the backbone of any isonitrile ligand to point directly away from the coordinated metal ion. Hence, isonitrile ligands by their very nature do not lend themselves to having the flexibility necessary to form a chelate ring.

Yamaguchi is silent on both ligands and chelating agents. The same is true of Schott Glaswerke and Walther. Hence, no combination of Crane/Yamaguchi/Schott Glaswerke/Walther can provide all the essential features of revised claim 1. Hence, the claimed subject matter is believed non-obvious over that combination of references. By definition, the same logic applies to dependent claims 2 to 14. The obviousness rejection to claims 1 to 14 should therefore be withdrawn.

The Examiner has also argued previously that the disclosures of both Yamaguchi and Schott Glaswerke are in the field of radiopharmaceuticals, and that hence both are properly combinable with Crane. Whilst that may be true for Yamaguchi, the Examiner is requested to cite specifically where in Schott Glaswerke any reference to radioisotopes and/or radiopharmaceuticals can be found to justify such an assertion. Applicants can find reference only to "...the storage of pharmaceutical or diagnostic solutions" and "blood or blood samples". Schott Glaswerke read without hindsight is silent on radioisotopes and formulations thereof used in medicine, ie. radiopharmaceuticals. Thus, Crane and Schott Glaswerke are not believed to be properly combinable, since they are clearly in very different fields of endeavor.

Walther refers to glass tubes having an interior coating thereon. Walther discloses that such tubes can have a wide range of possible uses (Column 1 lines 27-43 therein) – as would be expected of glass materials. The fact remains, however, that glass tubes *per se* are clearly in a completely different field of endeavor to radiopharmaceuticals. Hence, Walther also is not properly combinable with Crane.

The Examiner is also referred to [0014] of Yamaguchi. That describes very clearly that the  $^{201}\text{Tl}$  radiopharmaceutical is present as the uncomplexed, monovalent cation  $\text{Tl}^+$  and, as such, is in competition with the monovalent potassium ions ( $\text{K}^+$ ) of the glass:

"Since the thallium ions show the same properties as potassium ions, the potassium ions and thallium ions react with the glass competitively."

That is the mechanism described by Yamaguchi for the loss of  $^{201}\text{Tl}$  from solution to the glass. The person skilled in the art could have no expectation based on Yamaguchi that metal complexes of chelating agents would show “the same properties as potassium ions”. In fact, the logical conclusion must be that a metal complex of a chelating agent would behave very differently to potassium ion. Hence, the person skilled in the art could have no motivation to extend the teaching of Yamaguchi to metal complexes in the manner suggested by the Examiner. Hence, Yamaguchi and Crane also are not properly combinable in that regard.

The Examiner has also argued that the motivation to combine Yamaguchi and Crane stems from the advantages taught by Yamaguchi of providing a clear description of the vial contents. That is in clear contradiction of Yamaguchi, since Yamaguchi makes clear therein at eg. [0005], [0010], [0011] and [0016]-[0019] that such advantages are provided by reversed text lettering on the vial. That is a completely different feature to the silica coating. Since the Examiner contends that the person skilled in the art would be motivated to use such advantages, that leads to subject matter outside the scope of the present claims – since the combination would lead to radiopharmaceutical vials having the reversed lettering of Yamaguchi, not the silica coating.

For all the above reasons, the obviousness objection to claims 1-14 should be withdrawn. Favorable action thereon is respectfully requested.

**2. CLAIM REJECTIONS: 35 U.S.C. § 112.**

Previous claims 1-14 stand rejected as representing added matter due to the phrase 'non-radioactive organic ligand' being used instead of 'organic ligand'.

Revised claim 1 reinstates the previous claim language. This objection is therefore now believed moot. Applicants respectfully submit that the instant application, including claims 1-14, is in condition for allowance. Favorable action thereon is respectfully requested.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.16(j) or 37 CFR 1.136(a) which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Respectfully submitted,

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